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EXAMINER	
WOITACH, JOSEPH T	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/986,033	BUREAU ET AL.	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *85-89,91,95,96,98-102 and 104-120* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *85-89, 91, 95, 96, 98-102, 104-120* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application is a continuation of 09/341,350, filed July 9, 1999, now abandoned, which is a 371 National stage filing of PCT/FR98/01400, filed June 30, 1998.

Applicants' amendments filed March 23, 2004, has been received and entered. The specification has been amended. Claims 1-84, 90, 92-94, 97, 103 have been canceled. Claims 85, 86, 98, 99, 104, 107, 109, 111-117 have been amended. Claims 118-120 have been added. Claims 85-89, 91, 95, 96, 98-102, 104-120 are pending and currently under examination.

Election/Restriction

Applicant's election with traverse of Group IV , in Paper No. 12 was acknowledged. The restriction requirement was withdrawn because Examiner agreed that it would not constitute an undue burden to examine all the pending claims in light of the inventive concept of the claimed invention. Newly added claims 118-120 are drawn to the invention currently under examination.

Specification

The objection to the disclosure is withdrawn. The amendment to the specification to indicate that 09/341,350 has been abandoned has addressed the basis of the objection. See Applicants' amendment page 13, Section II.

Priority

The translation of the foreign priority papers has been made of record in accordance with 37 CFR 1.55 (see MPEP § 201.15) and overcomes the this rejection of Hoffman *et al.* because it antedates the cited reference.

It is noted that this application has been amended to recite benefit to US provisional application 60/067,488, filed December 1, 1997, and French application 97/08233 filed June 30, 1997.

It is required that a reference to the prior application must be inserted as the first sentence of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e) or 120. See 37 CFR 1.78(a). For benefit claims under 35 U.S.C. 120, the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of all nonprovisional applications. Also, the current status of all nonprovisional parent applications referenced should be included.

However, if the application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference to the prior application must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. This application was filed November 7, 2001. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the

pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A priority claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed claim for priority under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Therefore, while the claim for priority has been made in the first line of the specification, because of the filing date of the instant application and the date where the specification was amended to indicate the claim for priority, the appropriate petition must be filed. Accordingly, the priority date given the instant application is June 30, 1998, the date of the filing of the PCT application.

In addition, the amendment to the specification filed March 23, 2004, is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

The amendment which adds the priority claim in the first line of the specification recites that each application 'are incorporated by reference herein' is new matter because the amendment was not present and thus, not part of the original disclosure. Further, it is noted that the original declaration does not indicate or provide for the incorporation of these references. Therefore, the attempt to incorporate the entirety of the information from the priority documents as recited by the new amendment is considered new matter because this was not part of the original disclosure. See MPEP 608.04.

Applicant is required to cancel the new matter in the reply to this Office Action.

Oath/Declaration

Upon review of the declaration filed with the instant application, Examiner notes Applicants are correct and that the comments made by Examiner requiring clarification were made in error. The claim for benefit under 35 U.S.C. 119 were made to the French foreign application not the PCT application filed in France. See Applicants' amendment, page 13, Section III.

Information Disclosure Statement

The information disclosure statement filed March 23, 2004, fails to comply with 37 CFR 1.97(c) because it lacks a statement as specified in 37 CFR 1.97(e). It has been placed in the application

file, but the information referred to therein has not been considered. See Applicants' amendment, page 13, Section IV.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 90-94 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn.

Cancellation of the claims has rendered the specific basis of the rejections moot.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 85, 91, 98, 99, 100, 101, 102, 104-106, 111 and 118-120 are rejected under 35 U.S.C. 102(a) as being anticipate by Dev *et al.* (WO 96/39226).

Claims 85, 91, 98, 99, 100, 101, 102, 104-106, 111, and 118-120 are rejected under 35 U.S.C. 102(e) as being anticipate by Dev *et al.* (US Patent 5,993,434).

Applicants summarize the requirements of anticipation pointing to MPEP 2131 and citing *Richardson v. Suzuki Motor Co.* and *Scripps Clinic & Research Foundation v. Genetech, Inc.* in support . Summarizing the claim as amended Applicants argue that neither of the Dev *et al* references teach each and every element of the claims. Applicants argue that both Dev I and Dev II teach transfer into tumor cells at a field strength of 1000-1300 V/cm (bridging pages 15-16). Applicants argue that the present disclosure teaches that unexpectedly nucleic acids can be transferred into striated muscle cells *in vivo* with electrical pulses of 4 to 400 V/cm. See Applicants' amendment, starting on page 14, Section VI-A. Applicants arguments have been fully considered, but not found persuasive.

Initially, it is noted that claim 85 has been amended to be broader than originally set forth and is simply a method of transferring nucleic acids to one of more cells of striated muscle versus a method of promoting angiogenesis. The narrowing of the range of voltage used in the method is also noted.

First, it is noted that unexpected results or commercial success, is irrelevant to 35 U.S.C. 102 rejections, and thus cannot overcome a rejection so based (see MPEP 2131.04 and *In re Wiggins*, 488 F.2d 538, 543, 179 USPQ 421, 425 (CCPA 1973). To the end, that the specification provides a description of an affect of practicing a method not previously described for a particular condition would be immaterial to overcoming the rejection made under 35 USC 102 if the method has been described. Moreover, it is noted that the pending claims as amended do not require any particular amount of nucleic acid to be transferred, nor any amount of expression of the encoded factors. The present claims simply require practicing the method step of contacting a cell with a nucleic acid and electrically stimulating at least one striated muscle

cell in a range of 4 to 400 V/cm. Dependent claims indicate that the this can be as little as one pulse (claim 101) and that the duration of electrical stimulation (can) be greater than 10 milliseconds (claim 100), however other claims do not require even this duration. Again, the method as amended encompasses simply practicing the step specifically recited in the claim without any specific end or outcome required.

Second, respect to anticipation of the specific elements recited and encompassed by the claims, Applicants appear to rely on the fact that Dev *et al.* did not reduce to practice the invention as claimed. Examiner acknowledges the working example pointed to by Applicants, however this is simply one example reduced to practice by Dev *et al.* to demonstrate the methodology and not representative of the full disclosure in the teachings of Dev *et al.* provided by the description of the invention. As set forth in the basis of the rejection in the previous office action Dev *et al.* teaches that the methods can be used for delivery to a variety of cells including the cells of muscle (page 16, lines 22-26 and previous office action pages 6-7). It is noted that Dev *et al.* do not teach that the cells of muscle are striated muscle cells, however these are the only types of cells present in the muscle. Moreover, these cells can be differentiated from other types of muscle cells such as smooth muscle cells, such as those found in the colon, and cardiac muscle cells, which are also taught by Dev *et al.* Applicants argument that Dev *et al.* teach to transform tumor cells is not found persuasive because this teaching is present in only one working example, and in fact Dev *et al.* do teach delivery to the striated cells found in muscle.

Similarly, with respect to the voltages taught , Dev *et al.* teach to use an electrical field of 100V/cm to several kV/cm (page 10, lines 20-25 and column 7, lines 15-20). It is noted that Dev

et al. do not specifically teach the range of 4-400 V/cm as recited in the instant claims, however "[W]hen, as by a recitation of ranges or otherwise, a claim covers several compositions, the claim is anticipated' if one of them is in the prior art." (*Titanium Metals Corp. v.Banner,* 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985) (citing *In re Petering*, 301F.2d 676, 682, 133 USPQ 275, 280 (CCPA 1962)) and MPEP 2131.03). In this case the range of 100 to several kV/cm taught by Dev *et al.* is a range that encompasses and anticipates the claimed range. Moreover, it should be noted that subject matter encompassed by the prior art is anticipated unless there is evidence indicating such concentration or temperature is critical. ([W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)). To this end, Dev *et al.* teaches that the pulses can be set for various times and numbers of pulses (page 10, lines 10-15) and delivered in different waveforms (page 10, lines 10-15) and provides guidance for providing the optimum delivery with the minimum amount of peripheral damage to the cells (for example page 10, lines 3-9 and column 6, lines 58-67). For example, higher voltages result in higher amounts of heat and damage to cells surrounding the delivery device, therefore using lower voltages would result in less heat damage to surrounding cells (page 10). Further, there is no teaching away in Dev *et al.* for the use of voltages resulting in lower V/cm. To the contrary, Dev *et al.* provide detailed guidance in the prior art and the specifications of devices that can be used in the described methodology, for example the ECM 600 generator can provide 50-500 volts for LVM delivery (page 11, lines 5-10 and previous office action pages 6-7) and the T820 can be used to generate 100-300 volts at HVM setting and

50-500 boles at LVM setting (column 8, lines 5-10) a narrower range than generally disclosed and closer to that instantly claimed.

Newly added claims simply set forth that an angiogenic factor be expressed and a more narrow range of voltage be used or provided for a specific time, number of pulses or in a specific waveform. Applicants do not dispute that Dev *et al.* teach generally methods of delivering genes by using electroporation that can be used to affect gene therapy (page 2, lines 25-30 and top of page 10), or that Dev *et al.* teach that electroporation can be used to deliver polynucleotides, in particular sequences which encode an angiogenic compound such as Factor IX (page 15, lines 7-8 and column 10). In summary, Dev *et al.* provide guidance for the delivery of a polynucleotide to the cell of a muscle (a striated cell) and to use LVM ranges which anticipate the instant claims. The claims are anticipated by the teachings of Dev *et al.* because each of the limitations set forth in the claims are provided by Dev *et al.*

Claims 85, 104-106 and 111 rejected under 35 U.S.C. 102(e) as being anticipate by Hofmann *et al.* (US Patent 6,241,701) is withdrawn.

As noted above the translation of the foreign priority document has been received and entered. Upon review of the filing dates and the information in the priority document date, it is found that Hofmann *et al.* does not qualify as a 102(e) reference. See also Applicants' amendment pages 16-17, Section VIB.

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 85-89, 91, 95, 96, 98-102, 104-117and 118-120 are rejected under 35 U.S.C. 103(a) as being unpatentable over in view of Dev *et al.* (WO 96/39226 and 5,993,434), Wolff *et al.* (US Patent 5,693,622) and Wolff *et al.* (US Patent 6,228,844).

The anticipation of claims 85, 91, 98, 99, 100, 101, 102, 104-106, 111, and 118-120 rejected under 35 U.S.C. 102 by Dev *et al.* (WO 96/39226 and '434) is set forth above. Briefly, Dev *et al.* provides guidance for the *in vivo* delivery of a polynucleotide to the cell of a muscle (a striated cell) and to use LVM ranges for the expression of angiogenic factors in said cells to affect treatment in a subject. Dev *et al.* teach that the methods of electroporation can be adapted to delivery any polynucleotide for treatment while specifically teaching the delivery of polynucleotide sequences that encode angiogenic and hematopoietic factors. However, Dev *et al.* do not specifically set forth other the types of polynucleotide sequences useful in gene therapy treatments or the particular affects of expressing these sequences. At the time of filing Wolff *et al.* teach that gene therapy can be used for the delivery polynucleotide sequences

encoding a variety of proteins useful for treatment. Both disclosures of Wolff *et al.* are similar teaching that the cells of the muscle are a preferable cell type ('622 column 10 lines 4-40 and column 16, lines 50-53). Further, Wolff *et al.* teach that a variety of methods known in the art can be used for delivery including electroporation methodology ('622 column 16, lines 56-64). Finally, Wolff *et al.* teach that a variety of therapeutic proteins can be provided by gene therapy methods including the specific teaching for expressing growth hormones, GM-CSF, EPO ('622 column 15, lines 36-42) and VEGF ('844). Each Dev *et al.* and Wolff *et al.* teach that a polynucleotide sequence encoding any gene of interest can be delivered to affect the necessary treatment in a subject. Each teach that delivery can be accomplished by electroporation methodology *in vivo* to the cells of a tissue of interest including muscle, in particular Wolff *et al.* teach that the cells of the muscle are a preferred target cell. Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to use the electroporation for the delivery of a polynucleotide in methods of gene therapy. Further, given the broad guidance of each for the expression of any gene of interest and the specific examples of therapeutic genes known in the art to be therapeutic other genes not specifically taught nor recited in Dev *et al.*, and Wolff *et al.* would be considered obvious gene of interest to the artisan because they would be considered obvious adaptations to affect specific affects in a subject. For example, at the time of filing it was well established that the presence of NGF was capable of stimulating nerve growth. One having ordinary skill in the art would have been motivated to combine the teachings of Dev *et al.* and Wolff *et al.* because each specifically teach that electroporation can be used for the delivery of a gene of interest in gene therapy protocols. Further, each provide examples of and specific guidance for the expression of specific genes to

affect specific affects in a subject. There would have been a reasonable expectation of success to effectively combine the teaching of Dev *et al.* with that of Wolff *et al.* in light of the disclosure of the prior art for the successful use of electroporation *in vivo* and given the results of Wolff *et al.* for the ability to express a variety of genes of interest to affect treatment by gene therapy protocols.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

To the extent that Applicants arguments apply to the instant rejection, the requirements for making a rejection under 35 USC 103 are noted and addressed above. It is noted that Wolff *et al.* references only teach electroporation can be used and focuses primarily on direct injection, however this would not be considered teaching away. Wolff *et al.* acknowledge electroporation as a means of delivery known in the art, and the teachings relied upon in Wolff *et al.* is with respect to the specific form a treatment affected by gene therapy, not his delivery method. Taken in its entirety, the teaching of Wolff *et al.* provide the artisan a gene therapy method to express particular encoded genes in humans. The skilled artisan would be motivated to use any means of delivery taught by Wolff *et al.* and that is recognized in the art to have an advantage over other methods depending on the tissue to which the nucleic acid is delivered or to optimize the beneficial affect of the therapeutic methods. Review of the references provided by Applicants do not indicate that lower voltages would not work. Gilbert and Wells demonstrate that optimization of conditions is necessary. Further, the specific 'higher' voltages used in the methods disclosed by Gilbert and Wells correlate with the reduced amount of pulses/time that the voltage was administered. The skilled artisan would know that using lower voltages would require greater number of pulses or greater amount of time to result in the same result. These

aspects of optimization are clearly taught and set forth in Dev *et al.* and be obvious to the ordinary artisan. It is noted that Wolff *et al.* provide evidence that nucleic acids can be taken up by cells unaided by any other methodology, however this does not teach away from the fact that supplementary methodology would increase the uptake. Finally it is noted that unexpected results alone can overcome the basis of obviousness under 35 USC 103, however the instant claims do recite nor encompass any methodology that would result in an unexpected affect in there practice. The claims have been amended to simply a method for delivering a nucleic acid that encodes a protein, and do not require and are not drawn to any specific condition(s) set forth in the instant specification that result in unexpected outcomes.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (703) 308-2141.

Joseph T. Woitach

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